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ASSOCIATION BETWEEN MEASLES INFECTION AND THE OCCURRENCE OF CHRONIC INFLAMMATORY BOWEL DISEASE

Introduction

In 1993, the Inflammatory Bowel Disease Study Group of London, England, published an article describing the presence of particles suggesting measles virus in the intestinal tissues of patients suffering from Crohn's disease[1]. Other research was subsequently conducted on a possible link between infection by both wild and vaccinal strains of the measles virus and the occurrence of chronic inflammatory bowel disease (CIBD). A literature review was conducted to assess the biologic likelihood of the association, and the validity of microbiologic and epidemiologic arguments for or against a causal relationship. This issue is important because regular double-dose immunization programs along with catch-up measles vaccination campaigns directed toward school-age children have been implemented in several provinces.

Biologic likelihood

The measles virus may persistently infect certain cells lines in vitro. In vivo, the virus's persistence, in an altered form, has been observed in patients with subacute sclerosing panencephalitis (SSPE). The younger the age at which measles occurs, the greater the risk of SSPE. The measles virus thus has the genetic flexibility to persist in certain individuals and later trigger a chronic inflammatory infection. However, the incidence of SSPE seems to have declined with the introduction of measles vaccination programs, in contrast to Crohn's disease, the incidence of which is on the rise. Therefore, it must be postulated that the pathogenic mechanisms of these diseases are different. Intestinal tissues (epithelium, endothelium, and lymphoid tissue) become infected during measles, and the infection can be symptomatic. It is not known if such infection occurs following vaccination, but it is possible, even if an individual is symptomless. In vitro studies show that the tissue tropism of attenuated viruses is similar to that of the wild virus.

Microbiologic arguments

Five studies have been published on the association between measles infection and the occurrence of inflammatory bowel disease. The first is that of Miyamoto et al[2], which reported the presence of immunoreactive cells in the tissues of patients with Crohn's disease (n = 10). They used monoclonal antibodies that apparently reacted with the M protein of the measles virus. No such reactivity was observed in the tissues of patients with other inflammatory bowel diseases (n = 21). Such immunohistochemical data are difficult to interpret because less than half of the 25-patient sample with Crohn's disease was positive, and it is not known what proportion of patients had at least one test with positive results. Moreover, it is not known if those who read the test results were or were not aware of the origins of the samples.

In 1993, Wakefield et al[1] used transmission electron microscopy, immunohistochemistry, and in situ hybridization to study tissues from a small number of patients with Crohn's disease. Patients with ulcerative colitis, cancer, and intestinal tuberculosis were used as controls. Different controls were used for each technique. Giant cells, as well as particles resembling paramyxovirus (9/9), were found in Crohn granulomas using electron microscopy. None of these were found, however, among the controls (0/4). In situ hybridization, using a capsid gene probe, was positive in the case of Crohn's disease (10/10), but less so in the case of ulcerative colitis (4/10) or some other disease (3/10). Immunohistochemistry, using monoclonal antibodies directed against the capsid protein, was positive in 13 of the 15 cases of Crohn's disease, but negative in the two cases of tuberculosis. Positive reactions were localized in the nuclei of endothelial cells, macrophages, and occasionally lymphocytes. It is not known if

investigators were aware of the origins of the samples when the different tests were conducted. This is a major omission because interpretation of the results of these three techniques is subjective. Structures resembling viruses may be observed in many tissues (including those of mice free of any pathogenic agents) and they are a frequent artefact in electron microscopy. For example, a/β interferons induce formation of helico-tubular structures in cell nuclei. The results of in situ hybridization have not been quantified. The published photographs are far from impressive and one-third of the controls were positive. It is difficult to understand why the authors used the very simple technique of immunohistochemistry on only two of the controls. Although they claim that no reaction was observed in samples of normal tissues, this was not described in the article.

In 1995, Lewin et al[3] used immunogold electron microscopy to examine bowel tissue samples from six patients with Crohn's disease and two patients with intestinal tuberculosis. Using polyclonal antibodies against the capsid protein, they observed positive reactions in five of the six cases and in one of the two controls. Once again, interpretation of the results of this technique is subjective. It is not stated whether the observers were aware of sample origins. Results were not quantified and the published photographs were not convincing, except for those of the positive controls (SSPE cerebral tissue, acute measles appendicitis, and in vitro infection of vero cells).

In 1995, Knibbs et al[4] published the abstract of an electron microscopy study of three patients from a family with a history of Crohn's disease, and three controls matched for age and sex. They reported nuclear and cytoplasmic inclusions containing rows of tubular structures in endothelial cells, and macrophages of bowel tissues in three patients. The authors concluded that the structures observed were consistent with paramyxovirus capsids, but no photographs were available and they failed to say if the observations had been performed blind.

In 1995, Lizuka et al[5] used the chain polymerization technique to study 12 patients with Crohn's disease. Six had ulcerative colitis and 10 had non-inflammatory pathologies. Gene typing for N, H, F, and M genes of the measles virus was used to amplify and detect viral RNA. A positive result was observed only for the capsid coding gene, but the fragment-sequence study revealed no similarity with known sequences of the measles virus. The procedural details were not described in the abstract. This technique is the most sensitive and most specific for identifying the virus. The results suggest a virus other than measles could be present in Crohn's disease lesions.

Epidemiologic arguments

A total of four epidemiologic studies have been published on this topic. The first three were conducted by members of the Inflammatory Bowel Disease Study Group and the fourth by an independent group.

An initial epidemiologic study on the link between measles and chronic inflammatory bowel diseases was conducted using data collected in one region of Sweden[6]. During the 1945-1954 period, five epidemics of measles were identified from notifiable disease reports. An increased prevalence of Crohn's disease cases was observed for children born in the 3 months following the peak of the epidemic. Relative risk was 1.4. In this study, it was not possible to determine (with the exception of two cases) whether mothers or nursing infants had indeed contracted the disease during the perinatal period. No association was observed for ulcerative colitis.

In the second study, a cohort of individuals who had been immunized against measles (Schwarz strain) at ages of 10 to 24 months, as part of a randomized vaccine efficacy trial in 1964, were followed up annually by mail over 30 years[7]. Of 9,577 persons who had been initially vaccinated, 3,967 were traced and 3,545 agreed to complete a questionnaire. Medical records for 22 of the 28 individuals who reported a chronic inflammatory disease (Crohn's disease or ulcerative colitis) were reviewed and the diagnosis was confirmed in 19 cases. Four cases for which the files could not be verified were included in the analysis as confirmed cases.

A portion of the questionnaire was designed for the partner of the person who received the vaccine. It was not known, however, which of the two responded. Of the 2,541 questionnaires covering partners, 10 cases of chronic inflammatory disease were identified, although a history of vaccination or measles infection was not validated. A comparison of incidence between the vaccinated group and the partners shows a higher prevalence (not statistically significant) of Crohn's disease (RR = 2.0) and of ulcerative colitis (RR = 1.7). Another comparison was made between a cohort of children born in 1958 and monitored until the age of 31.

Of 11,407 individuals traced from the 17,417 initially recruited for the study, 19 cases of Crohn's disease or ulcerative colitis were identified through a self-administered questionnaire on chronic diseases. The method for confirming the diagnosis of these cases was not clearly explained. A comparison with the experimental group indicates a greater prevalence of cases among those vaccinated, with a statistically significant relative risk of 3.0 for Crohn's disease and 2.5 for ulcerative colitis. There are numerous sources of bias in this study that could explain the differences among the three groups. First, the group exposed to the virus and the two control groups did not come from the same population pools. The incidence of chronic inflammatory diseases can vary by place, dates of birth, age, and sex. These factors were not considered in the analysis. Second, only a small fraction of the experimental group was traced. It is possible that the likelihood of follow-up is linked to the health of those individuals. An individual who is ill with a chronic disease could be less likely to relocate and more inclined to respond to a questionnaire sent through the mail than someone in good health. The means of gathering and validating the information varied among the three groups. More information seems to have been collected from the study group than from the control groups (more general questions in one group and a questionnaire completed by the partner in the other). Furthermore, criteria used to established diagnoses were not given and it is not stated whether the final classification was made knowing to which of the three groups the subject belonged. Finally, it was hypothesized that vaccination or measles occurred at a later age in control groups than in the study group, but no evidence of this was provided.

In another study in the United Kingdom, a questionnaire was mailed to 16,875 members of two associations of patients with CIBD[8]. Recipients were asked to state their disease and birth date. They were also asked to give the birth date of an acquaintance of the same age who did not have their disease. The response rate was 21%. Birth-date distributions of those with a disease and of

controls born between 1950 and 1968 were compared on the basis of 10 measles epidemics that occurred during that period. Neither those with a disease nor the controls had been exposed to an epidemic during their mother's pregnancy or during their first year of life. The design of this study was similar to the Swedish one, but results diverged. The measles histories of those with CIBD and of the controls were unknown and it was not possible to refine the analysis.

Finally, a study compared statistics on the incidence of measles in the United Kingdom with that of Crohn's disease in three parts of that country from 1940 to 1990[9]. A gradual increase in the incidence of Crohn's disease had been observed since 1940, well before implementation of the measles immunization program began in 1968. This observation did not correspond with the hypothesis that cases were caused by vaccination at an early age. However, low risks may not be detected by this type of analysis.

Conclusion

That Crohn's disease and other chronic inflammatory illnesses of the intestine might be caused by a virus such as measles is an interesting hypothesis. Until the present time, microbiologic and epidemiologic arguments either for or against this hypothesis have not been very convincing. It is not very likely that other epidemiologic studies will provide conclusive evidence. In fact, it would be difficult to find a population that includes both individuals who have been exposed to the virus or to the vaccine and individuals who have not been exposed. However, new microbiologic studies might prove conclusive.

First, it would be necessary to demonstrate that the measles virus is indeed present in the lesions, that it is active, and that it contributes to inflammatory responses. Also, it would be necessary to prove that the pathogenic reaction can be induced by the wild virus and by the attenuated viruses present in vaccines. Strains and attenuation procedures vary from one manufacturer to another, and it is far from certain that all strains have the same ability to persist in tissues and to subsequently produce chronic inflammations. As was stated above, measles vaccine does not seem to be associated with SSPE, although the wild virus may be isolated (with difficulty) in patients with SSPE. The measles virus was isolated neither in patients with Crohn's disease or other chronic inflammatory diseases (Paget's disease, active chronic hepatitis, multiple sclerosis) in which a role for it has been claimed on morphologic, histologic or serologic grounds.

Current scientific data do not permit a causal link to be drawn between the measles virus and chronic inflammatory bowel diseases. While awaiting production and publication of other research, it would not be appropriate to alarm recipients of the vaccine by notifying them of this hypothetical risk, thus jeopardizing an immunization program of proven benefit.

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Editorial Comment

The review by Ward and DeWals questions the assertion by Wakefield et al. that early vaccination against measles leads to an increased risk of developing Crohn's disease and ulcerative colitis. The publication of what amounts to a weak epidemiologic study, in a prestigious journal such as the Lancet, caused understandable concern among some parents of children who had received or were about to receive measles vaccine. It also captured media attention in Canada where mass measles re-vaccination campaigns were being planned, and in the United Kingdom where a large scale immunization campaign to avert a predicted measles epidemic had been completed a short time earlier.

The public-health community was quick to respond with a critique of the study and to demonstrate work that refuted the article's claims. Wakefield himself, in fact, later published another piece of work that cast some doubt about the link between the measles vaccine and inflammatory bowel disease. However, whether the ultimate outcome of this work is positive or negative, it is secondary to the difficulties we face as a society in making rational use of scientific findings, particularly when it comes to the health and safety of our children.

The field of vaccine safety is a complex arena. Public health authorities do their best to implement programs that benefit the population as a whole. The balance of risk and benefit must weigh most heavily toward the side of benefit. Immunization programs have saved countless of children from death or disability while adding almost nothing to the burden of suffering. One only has to look at the eradication of smallpox and soon poliomyelitis to appreciate the value of immunization.

Today, the general public in industrialized countries does not bear the burden of disease or witness it. Not seeing disease, some are ready to stop immunizing immediately. Work that questions the safety of vaccines is enthusiastically supported, whether scientifically valid or not, and renews the resolve to ban them. This attitude is shortsighted however, since continued use of vaccines could eradicate some diseases one day. Only then can the need to vaccinate be eliminated.

The public-health community is also naturally very concerned about the safety of vaccines. It considers immunization to be a demonstrated benefit and concerns that arise about vaccine safety are something to take seriously, but to be evaluated carefully and always put in perspective. The public-health community would also like to stop vaccinating since it would mean that another disease had been eradicated and the burden of suffering from that disease had been eliminated for good.

There is nothing wrong with publishing hypotheses and speculations — it is the basis of scientific curiosity and the springboard to searching for the truth. We must be cautious, however, in accepting such information as evidence to rationalize action. The review by Ward and DeWals re-emphasizes the need for a critical examination of all new information. Such information, if taken in an uncritical fashion, has the potential to do more harm than good if it raises unjustified concerns.

RESPIRATORY VIRUS SURVEILLANCE
FluWatch Project

National influenza surveillance in Canada has historically relied on respiratory virus isolates submitted by approximately 24 laboratories across the country. Each province has at least one laboratory which reports weekly the number of isolates submitted, and the number confirmed as positive, to the Laboratory Centre for Disease Control (LCDC).

In addition to laboratory-based studies, some provinces collect information on other direct or indirect indicators of influenza

Figure 1
Influenza-like illness across Canada, reported by FluWatch, 1 October – 4 December 1996

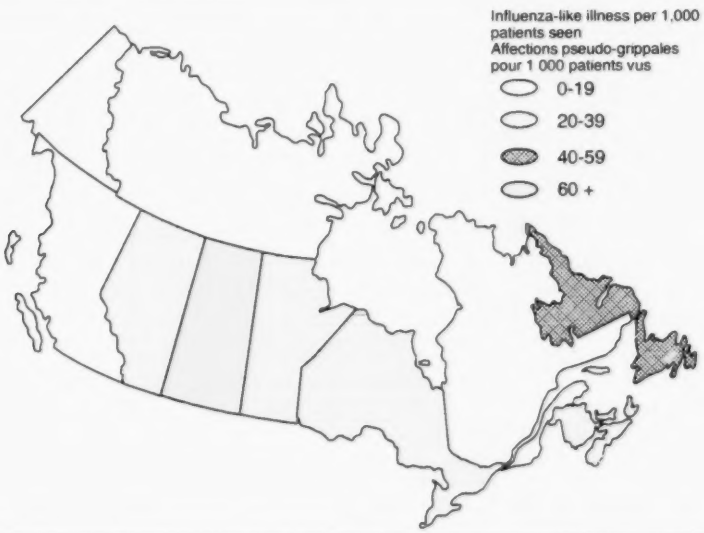

Table 1
Influenza-like illness across Canada, reported by FluWatch, 1 October – 4 December 1996

Influenza-like illness per 1,000 patients seen, by province and by week in 1996

Week	Nfld	PEI	NS	NB	QUE	ONT.	SASK.	ALTA	MAN.	BC
41-42	41	12.6	7.6	20.4	31.8	23.8	22.1	118.3	—	1.23
43-44	47.1	9.3	23.2	21.6	8.2	22.5	21.2	73.9	—	0.7
45-46	19.8	14.7	25.2	16	11.8	16.4	36.1	62.7	19.1	4
47-48	57.9	31.6	26.4	27.2	19.3	19.6	45.8	99.5	11.5	9.8

— Data not available
NB: Yukon reported 54.7 of ILI per 1,000 patients seen in week 45-46
Source: Division of Disease Surveillance, LCDC

activity. Such indicators include measuring absentees from school or place of employment, sentinel physician diagnosis rates, emergency-room presentations, hospital admissions, and of monitoring long-term care facility outbreaks.

From this information, LCDC evaluates influenza activity nationally and prepares weekly summary reports for dissemination. However, the existing national influenza surveillance system is limited by time delays in the processing and reporting of laboratory specimens, as well as province-to-province variations in ways of measuring influenza activity.

The FluWatch surveillance project, begun this season, is designed to enhance the existing national surveillance program by the timely collection of uniform data from across the country. The FluWatch project is a collaboration between The College of Family Physicians of Canada, National Recording System, sentinel physician reporting programs in British Columbia and Calgary, and LCDC. Sentinel physicians representing most census districts across Canada report weekly the number of consultations on one recording day each week, together with the number of cases fulfilling the case definition for influenza-like illness (ILI). The case definition is respiratory illness characterized by one or more of the following: cough, fever, chills, arthralgia, myalgia or prostration ***which in the opinion of the attending physician could be due to influenza virus.***

Every two weeks, data is compiled and combined with the available laboratory data and text into a FluWatch report which is sent to all participating physicians, provincial epidemiologists, virus laboratories, federal health authorities, Centres for Disease Control and Prevention, and the World Health Organization. It is hoped that FluWatch will assist these authorities to monitor and respond to changes in influenza morbidity and mortality by providing timely and consistent influenza data.

Currently 165 of 226 possible sentinel physicians have been recruited into FluWatch. In addition, over 40 physicians from British Columbia's and 5 from Alberta's sentinel sites also report into the system. The weekly response rate for recruited physicians rose steadily over the nine-week period to 58% by the end of week 47.

A summary of the data received between 1 October and 4 December 1996 is presented in this report. Figure 1 illustrates the standardized cumulative rates by province during the nine-week period. Saskatchewan, followed by Newfoundland, have the highest rates. Ten physicians reported from Saskatchewan during this period. Half of these doctors reported ILI on at least five separate occasions. Six doctors reported from Newfoundland in the nine-week period, however, only two reported seeing ILI on more than three occasions.

Table 1 presents the standardized rates by province for two-week periods after the initial week. Even with the removal of one physician with an outlying number of ILI, Saskatchewan's rates remain consistently higher than those found elsewhere in Canada. As of 7 December 1996, positive influenza A isolates were confirmed in British Columbia (18), Ontario (12), the Prairies (61) and Quebec (3). Influenza B isolates have been confirmed in the Atlantic region (1) and British Columbia (2).

Announcement

FIFTH CANADIAN PHARMACOEPIDEMIOLOGY FORUM
28-29 April 1997

Royal Connaught Howard Johnson Plaza-Hotel Hamilton, Ontario

Call for Abstracts

This two-day forum will focus on various current activities and issues in pharmacoepidemiology in Canada. In addition, the forum will be preceded by a workshop on interactive economic analysis to be held **27 April 1997**. Abstract topics should be related to population-based research on drugs and therapeutics. The deadline for submitting abstracts is **1 February 1997**.

For additional information and abstract forms, please contact **Dr. Ineke Neutel, Drugs Directorate, Health Canada, A.L. #1920A, Ottawa, Ontario, K1A 0L2, Telephone: (613) 954-6745, Fax: (613) 941-6458.**

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